AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph beginning on page 29, line 5, as follows:

~~Fig. 45 is~~ Figs. 45A and B are the *mus musculus* nucleic acid sequence for NM_008509 (SEQ ID NO:23).

Please amend the paragraph beginning on page 62, line 13, as follows:

Step 720. In optional step 720, a determination is made as to whether the cellular constituents in the candidate causative cellular constituent set are druggable. Hopkins and Groom, 2002, Nature Reviews 1, p. 727 provide one definition of a druggable target. To develop a definition of a druggable genome, Hopkins and Groom identified the molecular targets to rule-of-five compliant compounds. As put forth by Lipinski *et al.*, 1997, Adv. Drug Deliv. Rev. 23,3, a rule-of-five compliant synthetic compound (*e.g.*, compounds other than those derived from natural products) has less than five hydrogen-bond donors, the molecular mass of the compound is less than 500 Daltons, the lipophilicity is less than 5, and the sum of the nitrogen and oxygen atoms is less than 10. A thorough review of the literature by Hopkins and Groom identified 399 non-redundant molecular targets that have been shown to bind rule-of-five compliant compounds with binding affinities below 10 μM. Next, Hopkins and Groom took the drug-binding domains of the 399 non-redundant molecular targets and determined the families that they represent, as captured by their InterPro domain (Hopkins and Groom, 2002, Nature Reviews 1, p. 727; Apweiler *et al.*, 2001, Nucleic Acids Res. 29,37). A total of 130 protein families represent the 399 non-redundant molecular targets. These protein families are provided in the online supplemental information for Hopkins and Groom, 2002, Nature Reviews Drug Discovery 1, p. 727 at ~~www.nature.com/reviews/drugdise~~ nature.com/reviews/drugdisc and include G-protein coupled receptors, serine/threonine and tyrosine protein kinases, zinc

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metallo-peptidases, serine proteases, nuclear hormone receptors and phosphodiesterases. Thus, in one embodiment of the present invention step 720 comprises determine whether each cellular constituent in the candidate causative cellular constituent set includes a druggable domain as defined by Hopkins and Groom.

Please amend the paragraph beginning at page 97, line 16, as follows:

Other suitable sources of genetic markers include databases that have various types of gene expression data from platform types such as spotted microarray (microarray), high-density oligonucleotide array (HDA), hybridization filter (filter) and serial analysis of gene expression (SAGE) data. Another example of a genetic database that can be used is a DNA methylation database. For details on a representative DNA methylation database, see Grunau *et al.*, in press, MethDB- a public database for DNA methylation data, *Nucleic Acids Research*; or the URL: ~~http://genome.imb-jena.de/public.html~~ genome.imb-jena.de/public.html.

Please amend the paragraph beginning at page 97, line 24, as follows:

In one embodiment of the present invention, a set of genetic markers is derived from any type of genetic database that tracks variations in the genome of an organism of interest. Information that is typically represented in such databases is a collection of locus within the genome of the organism of interest. For each locus, strains for which genetic variation information is available are represented. For each represented strain, variation information is provided. Variation information is any type of genetic variation information. Representative genetic variation information includes, but is not limited to, single nucleotide polymorphisms, restriction fragment length polymorphisms, microsatellite markers, restriction fragment length

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polymorphisms, and short tandem repeats. Therefore, suitable genotypic databases include, but are not limited to:

Genetic variation type	Uniform resource location
SNP	~~http://bioinfo.pal.roche.com/usuka_bioinformatics/cgi-bin/msnp/msnp.pl~~ bioinfo.pal.roche.com/usuka_bioinformatics/cgi-bin/msnp/msnp.pl
SNP	~~http://snp.cshl.org/~~ snp.cshl.org/
SNP	~~http://www.ibc.wustl.edu/SNP/~~ ibc.wustl.edu/SNP/
SNP	~~http://www-genome.wi.mit.edu/SNP/mouse/~~ genome.wi.mit.edu/SNP/mouse/
SNP	~~http://www.ncbi.nlm.nih.gov/SNP/~~ ncbi.nlm.nih.gov/SNP/
Microsatellite markers	~~http://www.informatics.jax.org/searches/polymorphism_form.shtml~~ informatics.jax.org/searches/polymorphism_form.shtml
Restriction fragment length polymorphisms	~~http://www.informatics.jax.org/searches/polymorphism_form.shtml~~ informatics.jax.org/searches/polymorphism_form.shtml
Short tandem repeats	~~http://www.cidr.jhmi.edu/mouse/mmset.html~~ cidr.jhmi.edu/mouse/mmset.html
Sequence length polymorphisms	~~http://mcbio.med.buffalo.edu/mit.html~~ mcbio.med.buffalo.edu/mit.html
DNA methylation database	~~http://genome.imb-jena.de/public.html~~ genome.imb-jena.de/public.html
Short tandem-repeat polymorphisms	Broman *et al.*, 1998, Comprehensive human genetic maps: Individual and sex-specific variation in recombination, American Journal of Human Genetics 63, 861-869
Microsatellite markers	Kong *et al.*, 2002, A high-resolution recombination map of the human genome, Nat Genet 31, 241-247

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Please amend the paragraph beginning at page 98, line 2, as follows:

In addition, the genetic variations used by the methods of the present invention may involve differences in the expression levels of genes rather than actual identified variations in the composition of the genome of the organism of interest. Therefore, genotypic databases within the scope of the present invention include a wide array of expression profile databases such as the one found at the URL: ~~http://www.ncbi.nlm.nih.gov/geo/~~ ncbi.nlm.nih.gov/geo/.

Please amend the paragraph beginning at page 141, line 5, as follows:

Many known programs can be used to perform linkage analysis in accordance with this aspect of the invention. One such program is MapMaker/QTL, which is the companion program to MapMaker and is the original QTL mapping software. MapMaker/QTL analyzes F_2 or backcross data using standard interval mapping. Another such program is QTL Cartographer, which performs single-marker regression, interval mapping (Lander and Botstein, *Id.*), multiple interval mapping and composite interval mapping (Zeng, 1993, PNAS 90: 10972-10976; and Zeng, 1994, Genetics 136: 1457-1468). QTL Cartographer permits analysis from F_2 or backcross populations. QTL Cartographer is available from ~~http://statgen.ncsu.edu/qtlcart/cartographer.html~~ statgen.ncsu.edu/qtlcart/cartographer.html (North Carolina State University). Another program that can be used by processing step 114 is Qgene, which performs QTL mapping by either single-marker regression or interval regression (Martinez and Curnow 1994 Heredity 73:198-206) . Using Qgene, eleven different population types (all derived from inbreeding) can be analyzed. Qgene is available from ~~http://www.qgene.org/~~ qgene.org/. Yet another program is MapQTL, which conducts standard interval mapping (Lander and Botstein, *Id.*), multiple QTL mapping (MQM) (Jansen, 1993, Genetics 135: 205-211; Jansen, 1994, Genetics 138: 871-881), and nonparametric mapping

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(Kruskal-Wallis rank sum test). MapQTL can analyze a variety of pedigree types including outbred pedigrees (cross pollinators). MapQTL is available from Plant Research International, Plant Research International, P.O. Box 16, 6700 AA Wageningen, The Netherlands; ~~Zttp://www.plant.wageningen-ur.nl/default.asp?section=products~~ plant.wageningen-ur.nl /default.asp?section=products). Yet another program that may be used in some embodiments of processing step 210 is Map Manager QT, which is a QTL mapping program (Manly and Olson, 1999, Mamm Genome 10: 327-334). Map Manager QT conducts single-marker regression analysis, regression-based simple interval mapping (Haley and Knott, 1992, Heredity 69, 315-324), composite interval mapping (Zeng 1993, PNAS 90: 10972-10976), and permutation tests. A description of Map Manager QT is provided by the reference Manly and Olson, 1999, Overview of QTL mapping software and introduction to Map Manager QT, Mammalian Genome 10: 327-334.

Please amend the paragraph beginning at page 142, line 8, as follows:

Still another program that can be used to perform linkage analysis is QTL Café. The program can analyze most populations derived from pure line crosses such as F_2 crosses, backcrosses, recombinant inbred lines, and doubled haploid lines. QTL Café incorporates a Java implementation of Haley & Knotts' flanking marker regression as well as Marker regression, and can handle multiple QTLs. The program allows three types of QTL analysis single marker ANOVA, marker regression (Kearsey and Hyne, 1994, Theor. Appl. Genet., 89: 698-702), and interval mapping by regression, (Haley and Knott, 1992, Heredity 69: 315-324). QTL Café is available from ~~http://web.bham.ac.uk/g.g.seaton/~~ web.bham.ac.uk/g.g.seaton/.

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Please amend the paragraph beginning at page 142, line 17, as follows:

Yet another program that can be used to perform linkage analysis is MAPL, which performs QTL analysis by either interval mapping (Hayashi and Ukai, 1994, Theor. Appl. Genet. 87:1021-1027) or analysis of variance. Different population types including F_2, back-cross, recombinant inbreds derived from F_2 or back-cross after a given generations of selfing can be analyzed. Automatic grouping and ordering of numerous markers by metric multidimensional scaling is possible. MAPL is available from the Institute of Statistical Genetics on Internet (ISGI), Yasuo, UKAI, ~~http://web.bham.ac.uk/g.g.seaton/~~ web.bham.ac.uk/g.g.seaton/.

Please amend the paragraph beginning at page 142, line 24, as follows:

Another program that can be used for linkage analysis is R/qtl. This program provides an interactive environment for mapping QTLs in experimental crosses. R/qtl makes uses of the hidden Markov model (HMM) technology for dealing with missing genotype data. R/qtl has implemented many HMM algorithms, with allowance for the presence of genotyping errors, for backcrosses, intercrosses, and phase-known four-way crosses. R/qtl includes facilities for estimating genetic maps, identifying genotyping errors, and performing single-QTL genome scans and two-QTL, two-dimensional genome scans, by interval mapping with Haley-Knott regression, and multiple imputation. R/qtl is available from Karl W. Broman, Johns Hopkins University, ~~http://biosun01.biostat.jhsph.edu/~kbroman/qtl/~~ biosun01.biostat.jhsph.edu /~kbroman/qtl/.

Please amend the paragraph beginning at page 143, line 26, as follows:

In some embodiments of the present invention, linkage analysis is performed using the algorithm of Lander, as implemented in programs such as GeneHunter. See, for example,

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Kruglyak *et al.*, 1996, Parametric and Nonparametric Linkage Analysis: A Unified Multipoint Approach, American Journal of Human Genetics 58:1347-1363, Kruglyak and Lander, 1998, Journal of Computational Biology 5:1-7; Kruglyak, 1996, American Journal of Human Genetics 58, 1347-1363. In such embodiments, unlimited markers may be used but pedigree size is constrained due to computational limitations. In other embodiments, the MENDEL software package is used. (See ~~http://bimas.dcrt.nih.gov/linkage/ltools.html~~ bimas.dcrt.nih.gov /linkage/ltools.html). In such embodiments, the size of the pedigree can be unlimited but the number of markers that can be used in constrained due to computational limitations. The techniques described in this Section typically require an inbred population.

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